BERTINORO ULTRASUONI

XXI CORSO NAZIONALE DI

ULTRASONOLOGIA VASCOLARE

DIAGNOSI E TERAPIA

Bertinoro,

20-22 aprile 2023

Centro Residenziale Universitario

Valutazione della risposta al trattamento con anticoagulanti in pazienti affetti da neoplasie solide o ematologiche e contemporanea diagnosi di tromboembolismo venoso

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Il tromboembolismo venoso (TEV) rappresenta una delle principali cause di morbilità e mortalità ospedaliera ed i **pazienti neoplastici** rappresentano circa il **20% dei casi complessivi di TEV**.

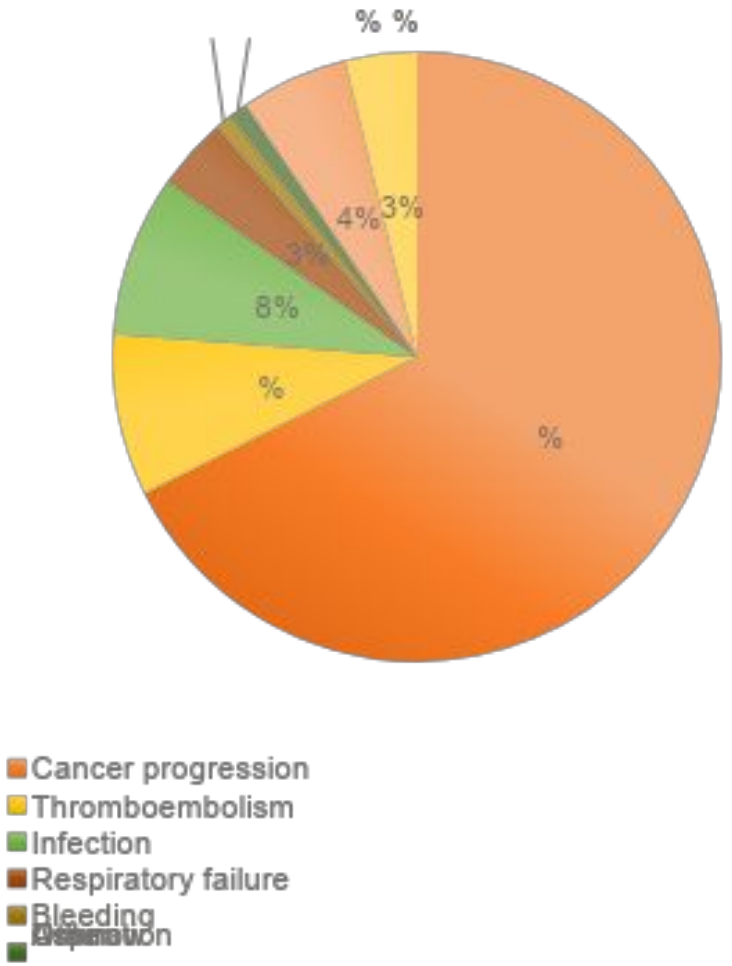


Figure 1. Leading cause of death in cancer patients - *Epidemiology of cancer-associated venous thrombosis*. *Timp JF et al. Blood. 2013*

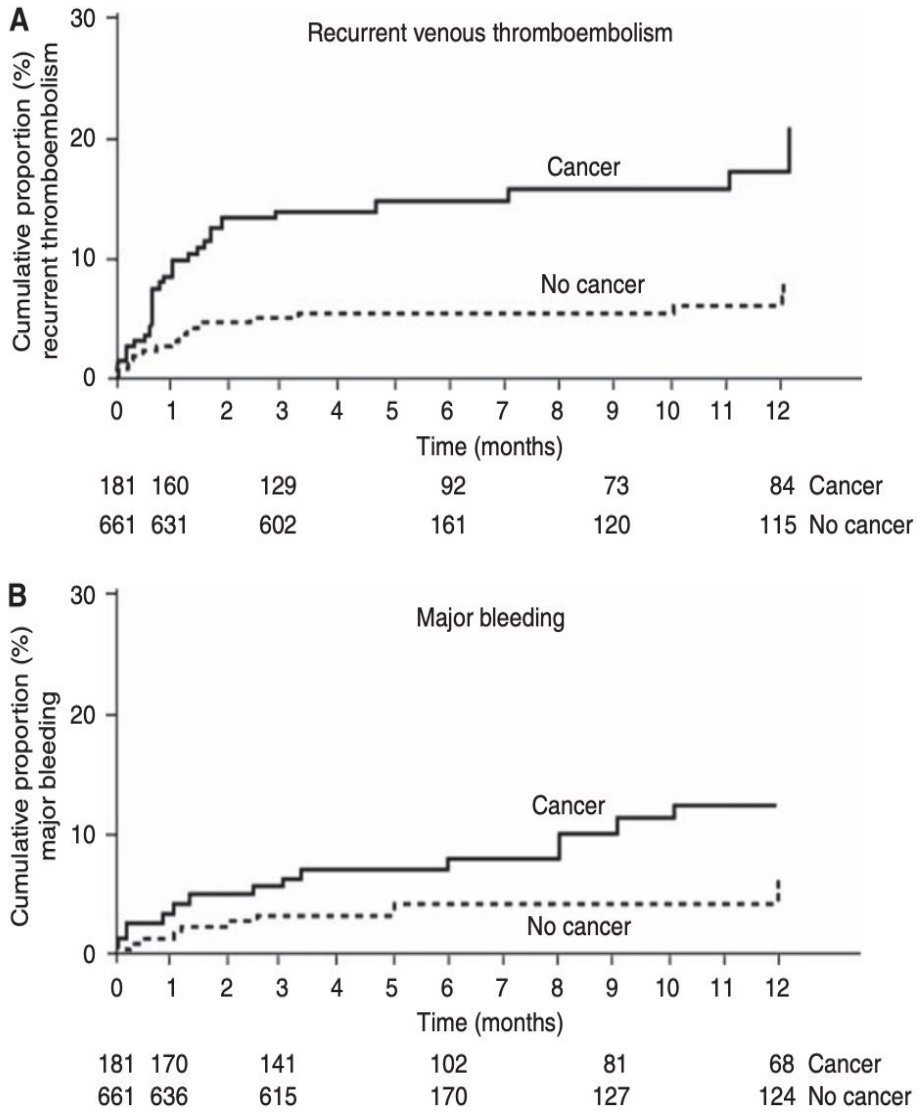


Figure 2.
(A) Cumulative incidence of **recurrent VTE during anticoagulation therapy** among patients with and without cancer
(B) Cumulative incidence of **bleeding** during anticoagulant therapy
Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Prandoni P et al. Blood. 2002*

Table 3. Absolute and relative rates of thromboembolic events in different molecular driver cohorts

	N	Patients with TE	Total[a] events	Person-time (years)	Incidence rate—arterial and venous (per 1000 person-years)	95% CI		Relative incidence rate[b]	95% CI		Incidence rate—venous (per 1000 person-years)	Incidence rate—arterial (per 1000 person-years)[c]
						Lower	Upper		Lower	Upper		
ROS1	44	11 (25%)	12	111.1	99.0	56.5	173.4	1	—	—	99.0	9.0
ALK	98	36 (36.7%)	41	391.8	91.9	67.3	125.4	1.192 ($P = 0.61$)	0.60	2.36	79.1	12.8
EGFR	168	38 (22.6%)	44	460.6	82.5	60.8	111.9	0.956 ($P = 0.90$)	0.47	1.94	49.9	34.7

Patient-related risk factors

- Medical co-morbidities (CCI ≥3)
- Presence of varicose veins
- Prior VTE
- Hereditary risk factors (e.g. Factor V Leiden)

Tumour-related risk factors

- Site of cancer
  - Very high risk: stomach, pancreas, brain
  - High risk: lung, haematological, gynaecological, renal, bladder
- Histological grade of the tumour
- Stage of cancer/metastases
- Time since cancer diagnosis

Treatment-related risk factors

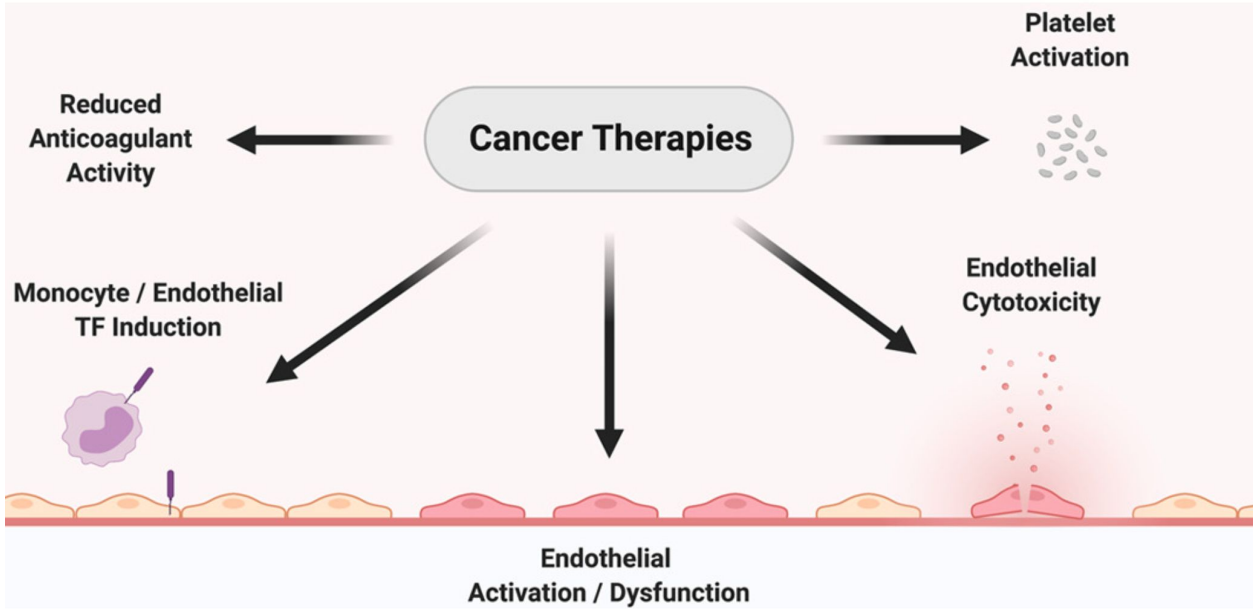
- Platinum-based and other chemotherapy
- Anti-angiogenesis agents
- Hormonal therapy
- Surgery
- Radiotherapy
- Blood transfusion
- Central venous catheters
- Immobility and hospitalization

Biomarkers

- Haematological biomarkers (e.g. platelet, haemoglobin, leukocyte counts)
- D-dimer, P-selectin
- Prothrombin fragment 1 + 2
- Thrombin generation potential
- Microparticle tissue factor activity
- C-reactive protein

The cumulative incidence of venous and arterial TEs throughout the cancer course **was higher** in patients with **ROS1+** and **ALK+** NSCLC.

Risk of thromboembolism in non-small-cell lung cancers patients with different oncogenic drivers, including ROS1, ALK, and EGFR mutations. *H.-Y. Wang et al.*



Cancer Therapy–Associated Thrombosis.
Steven P. Grover et al. AHA/ASA Journal

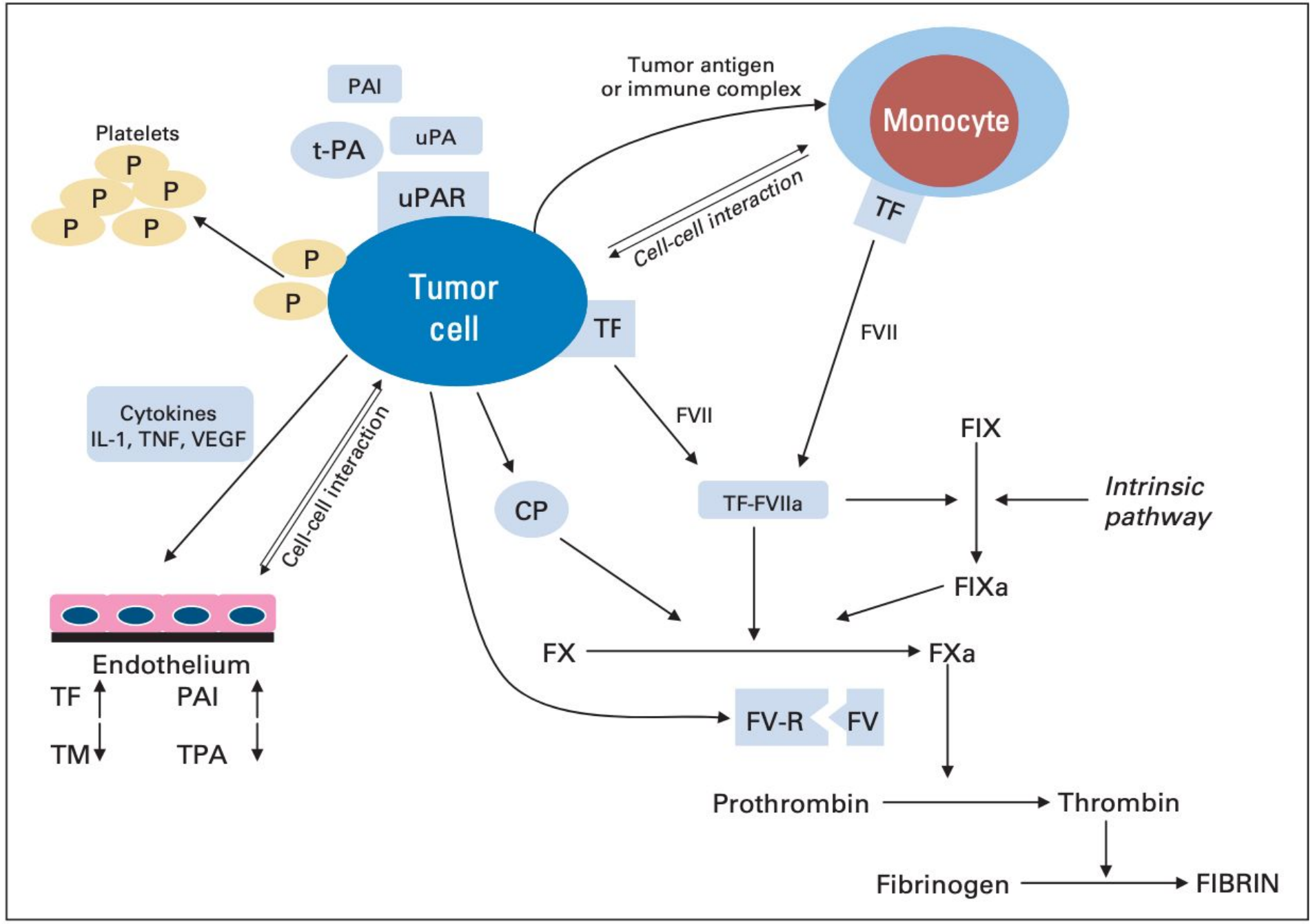


Fig 1. The tumor cell promotes a hypercoagulable state and activates the hemostatic system, utilizing cell surface proteins such as tissue factor (TF), cancer procoagulant (CP), tissue plasminogen activator (t-PA), urokinase plasminogen activator (uPA), as well as plasminogen activator inhibitor 1 (PAI-1) and 2 (PAI-2). Interaction with other blood cells (eg, monocytes, platelets, endothelial cells) occurs (A) directly by cell-cell interaction; or (B) indirectly by cytokine release promoting prothrombotic endothelial changes. IL, interleukin; P, protein; F, factor; TM, thrombomodulin; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; R, receptor; FV-R, factor V receptor. Adapted from Falanga.[5]

Abdol Razak NB et al. ***An Overview of Mechanisms, Risk Factors, and Treatment****. Cancers (Basel). 2018*

Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer

Agnes Y.Y. Lee, M.D., Mark N. Levine, M.D., Ross I. Baker, M.D., Chris Bowden, M.D., Ajay K. Kakkar, M.B., Martin Prins, M.D., Frederick R. Rickles, M.D., Jim A. Julian, M.Math., Susan Haley, B.Sc., Michael J. Kovacs, M.D., and Michael Gent, D.Sc. for the Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators*

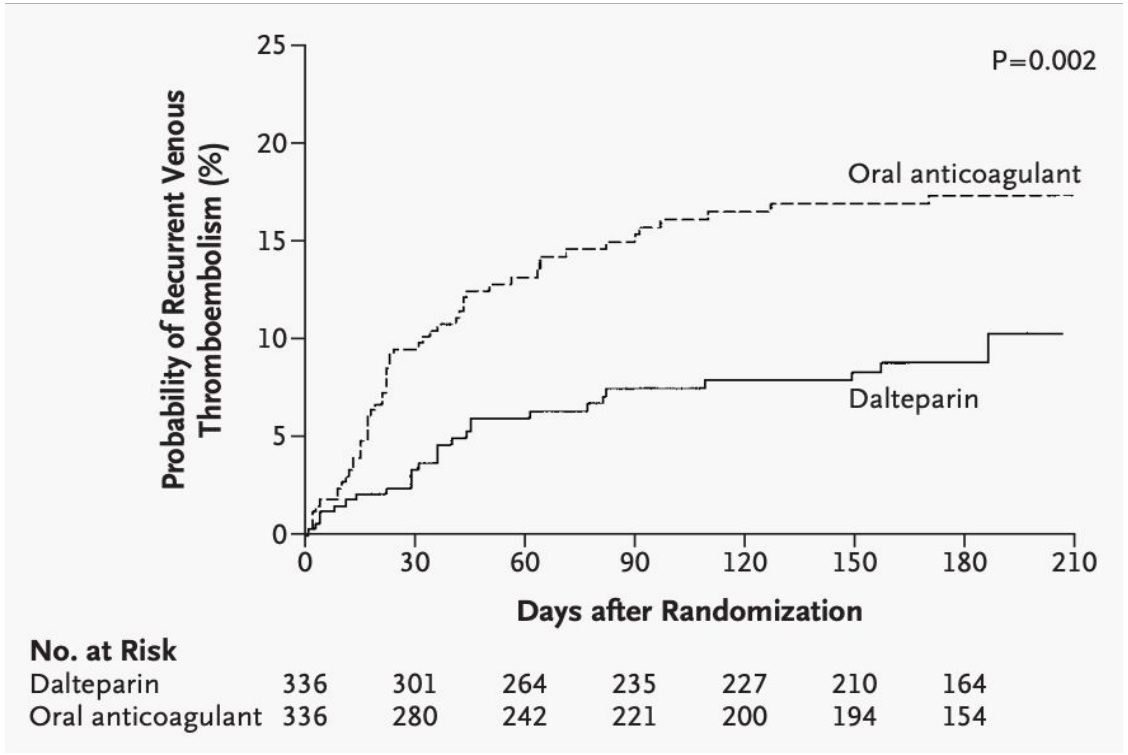


Figure 1. Kaplan–Meier Estimates of the Probability of Symptomatic Recurrent Venous Thromboembolism among Patients with Cancer, According to Whether They Received Secondary Prophylaxis with Dalteparin or Oral Anticoagulant Therapy for Acute Venous Thromboembolism.

An event was defined as an objectively verified, symptomatic episode of recurrent deep-vein thrombosis, pulmonary embolism, or both during the six-month study period. The hazard ratio for recurrent thromboembolism in the dalteparin group as compared with the oral-anticoagulant group was 0.48 (95 percent confidence interval, 0.30 to 0.77; P=0.002 by the log-rank test).

*In patients with cancer and acute venous thromboembolism, **dalteparin was more effective** than VKa **in reducing the risk of recurrent thromboembolism** without increasing the risk of bleeding.*

Name of the study	Type of Patients included	Treatment allocation Intervention	Treatment allocation Control	Primary Outcome
CANVAS	Patients with cancer and acute VTE	**Any DOAC** at discretion of treating investigator in accordance with the drug's FDA package insert	**Any approved LMWH** at the discretion of the treating investigator in accordance with the drug's FDA package insert	Efficacy: recurrent VTE Safety: major bleeding
CARAVAGGIO	Patients with active or recent cancer and acute DVT or PE	**Apixaban** 10mg twice daily for 7 days, followed by 5mg twice daily	**Dalteparin** 200IU/Kg once daily for 1 month followed by 150IU/Kg once daily	Efficacy: recurrent VTE Safety: major bleeding
CASTA-DIVA	Patients with active cancer and acute DVT or PE at high risk of recurrent VTE	**Rivaroxaban** 15mg twice daily for 21 days followed by 20mg once daily	**Dalteparin** 200IU/Kg once daily for 1 month followed by 150IU/Kg once daily	Efficacy: composite of recurrent VTE and worsening of pulmonary vascular or venous obstruction on systematic examinations Safety: major bleeding
ADAM-VTE	Active cancer patient with acute DVT (including upper extremity), PE, splanchnic or cerebral vein thrombosis	**Apixaban** 10mg twice daily for 7 days, followed by 5mg twice daily	**Dalteparin** 200IU/Kg once daily for 1 month followed by 150IU/Kg once daily	Major bleeding including fatal bleeding
HOKUSAI-VTE CANCER	Patients with active cancer and symptomatic or incidental popliteal, femoral or iliac or IVC DVT, symptomatic or incidental PET	Therapeutic dose of LMWH for at least 5 days followed by **Edoxaban** 60 or 30mg once daily	**Dalteparin** 200IU/Kg once daily for 1 month followed by 150IU/Kg once daily	Composite of recurrent VTE or major bleeding
SELECT-D	Patients with active cancer and symptomatic DVT, symptomatic PE, or incidental PE	**Rivaroxaban** 15mg twice daily for 21 days, followed by 20mg once daily	**Dalteparin** 200IU/Kg once daily for 1 month followed by 150IU/Kg once daily	Recurrent VTE

European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis.
Eur J Vasc Endovasc Surg. 2021

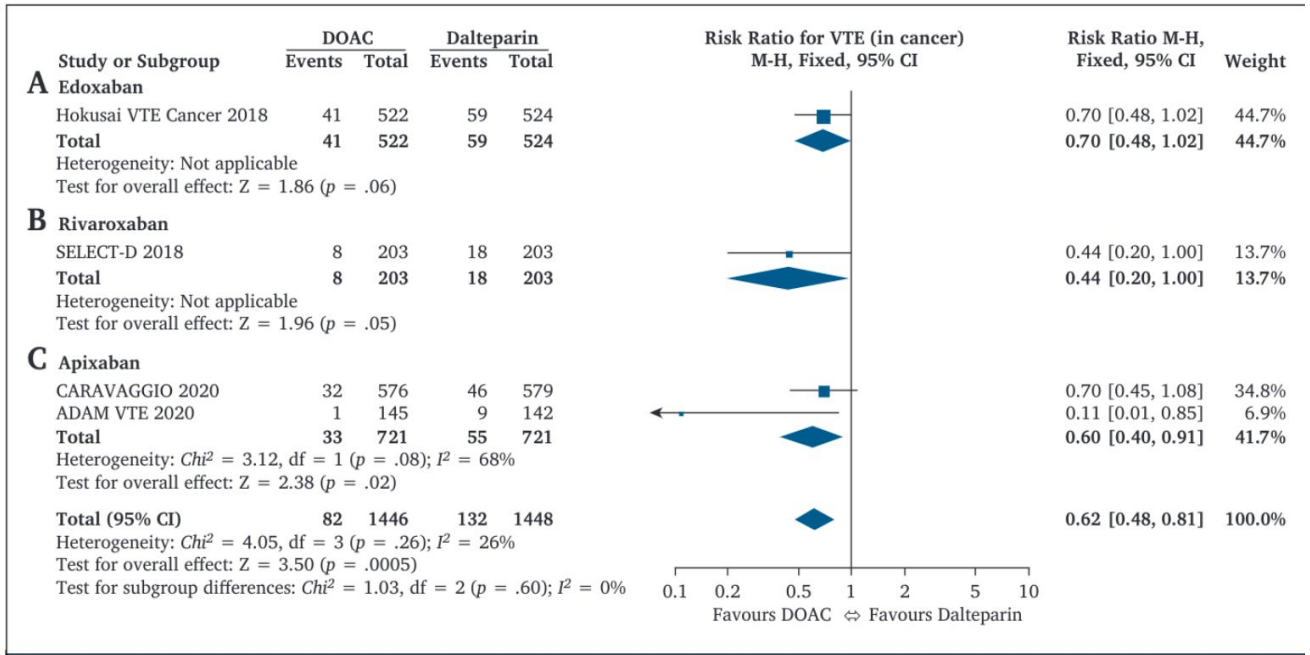


Figure 12. Forest plot analysis of randomised controlled trials comparing a direct oral anticoagulant (DOAC), (A) edoxaban, (B) rivaroxaban, or (C) abixaban, with dalteparin for cancer associated venous thrombosis, regarding the outcome of venous thromboembolism (VTE). M-H = Mantel–Haenszel; CI = confidence interval; ADAM = Apixaban and Dalteparin in Active Malignancy.

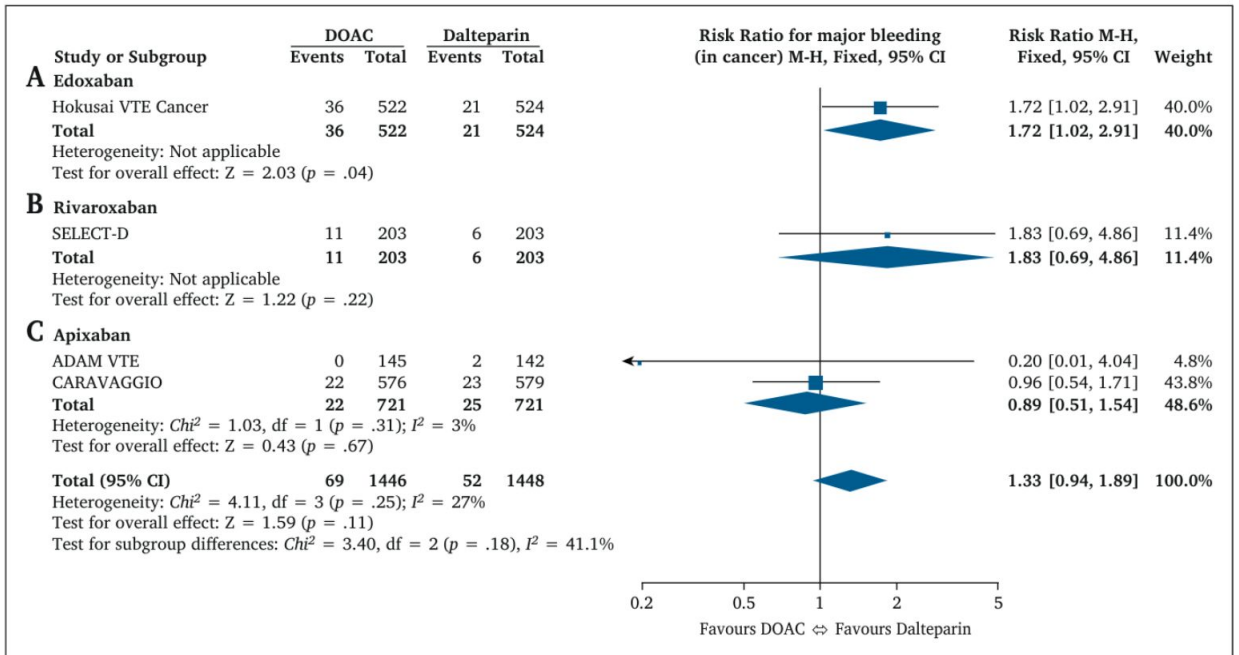


Figure 13. Forest plot analysis of randomised controlled trials comparing a direct oral anticoagulant (DOAC), (A) edoxaban, (B) rivaroxaban, or (C) abixaban, with dalteparin for cancer associated venous thrombosis, regarding the outcome of major bleeding. M-H = Mantel–Haenszel; CI = confidence interval; VTE = venous thromboembolism; ADAM = Apixaban and Dalteparin in Active Malignancy.

Importantly, bleeding was more common in patients with gastrointestinal (GI) malignancies receiving **Edoxaban** or **Rivaroxaban** compared with LMWHs, while apixaban was not associated with an increased risk of bleeding in these patients.

Frere C et al. ***Direct oral anticoagulant versus low molecular weight heparin for the treatment of cancer-associated venous thromboembolism****: 2022 updated systematic review and meta-analysis of randomized controlled trials. J Hematol Oncol. 2022*

Recommendation 63

For patients with cancer associated deep vein thrombosis, a low molecular weight heparin is recommended for initial and principal phase anticoagulation.

Class	Level	Reference
I	A	Kirkilesis *et al.* (2019)[365]

Recommendation 64

For patients with active cancer associated deep vein thrombosis, switching from a low molecular weight heparin to an oral anticoagulant is recommended after three to six months of treatment for extended treatment.

Class	Level	Reference
I	C	Consensus

Recommendation 65

In selected patients with cancer associated deep vein thrombosis, with the malignancy not located in the gastrointestinal or genitourinary systems, an approved direct oral anticoagulant for initial, principal, and extended treatment should be considered.

Class	Level	References
IIa	A	Posch *et al.* (2015),[364] Kirkilesis *et al.* (2019),[365] Kraaijpoel *et al.* (2018),[367] McBane *et al.* (2020),[369] Agnelli *et al.* (2020)[370]

European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. *Eur J Vasc Endovasc Surg. 2021*

Clinical Question 4. What is the best method for treatment of patients with cancer with established VTE to prevent recurrence?

Recommendation 4.1. Initial anticoagulation may involve LMWH, UFH, fondaparinux, or rivaroxaban. For patients initiating treatment with parenteral anticoagulation, LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the patient with cancer with newly diagnosed VTE who does not have severe renal impairment (defined as creatinine clearance less than 30 mL/min) (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.2. For long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred because of improved efficacy over vitamin K antagonists (VKAs). VKAs are inferior but may be used if LMWH or direct oral anticoagulants (DOACs) are not accessible. There is an increase in major bleeding risk with DOACs, particularly observed in GI and potentially genitourinary malignancies. Caution with DOACs is also warranted in other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked prior to using a DOAC (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.3. Anticoagulation with LMWH, DOACs, or VKAs beyond the initial 6 months should be offered to select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy. Anticoagulation beyond 6 months needs to be assessed on an intermittent basis to ensure a continued favorable risk-benefit profile (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak to moderate).

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ***ASCO Clinical Practice Guideline Update***

Table 5 Effect of drug-drug interactions and clinical factors on NOAC plasma levels and anticoagulant effects

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[519]

CAT-Ther: Protocollo

DISEGNO DELLO STUDIO

Lo studio si classifica come **osservazionale** con l'utilizzo di farmaco, **spontaneo**, **monocentrico**, **retrospettivo** e **prospettico** per i pazienti con diagnosi di tromboembolismo venoso in corso di neoplasia, afferenti *all'SSD Angiologia e Malattie della Coagulazione dell'IRCCS Azienda Ospedaliero-Universitaria di Bologna.*

CRITERI DI INCLUSIONE e POPOLAZIONE DELLO STUDIO

- età ≥ 18 aa
- diagnosi di trombosi venose in qualsiasi sede
- diagnosi di trombosi venose CVC relate
- diagnosi di embolia polmonare sia sintomatica che incidentale
- diagnosi di neoplasia solida o ematologica in trattamento o attiva
- ottenimento del Consenso Informato

AMPIEZZA DELLA POPOLAZIONE DELLO STUDIO e POTENZA STATISTICA

Tenendo conto che l'afferenza mensile dei pazienti presso l'Ambulatorio Consulenze dell'SSD Angiologia e Malattie della Coagulazione dell'IRCCS AOUBO si attesta su circa 50 pazienti, sulla base dei criteri di inclusione/esclusione, **si stima di poter arruolare circa 500 pazienti**.

DURRATA DELLO STUDIO

La fine dello studio, comprensiva di analisi dati, è prevista per il 31/12/2025. La durata dello studio, compresa tra l'inizio dell'arruolamento dei pazienti e la fine dell'analisi dei dati sarà di 34 mesi.

OBIETTIVO **PRIMARIO**

Valutare la **frequenza di recidive trombotiche e complicanze emorragiche** durante trattamento con EBPM o DOACs nei pazienti con tromboembolismo venoso e neoplasie solide ed ematologiche ambulatoriali seguiti presso l'SSD Angiologia e Malattie della Coagulazione dell'IRCCS AOUBO, a seguito dell'inizio di terapia anticoagulante.

OBIETTIVO **SECONDARIO**

Identificare i **fattori di rischio** per complicanze emorragiche e per rischio emorragico in corso di trattamento anticoagulante per CAT.
Valutare l'**applicabilità** e l'**affidabilità di uno score**, ad oggi non in uso nella pratica clinica in una coorte prospettica di pazienti con CAT.

ESITI

- Recidiva di trombosi venosa profonda e/o embolia polmonare durante la terapia anticoagulante (sia EBPM che DOACs)
- Complicanze emorragiche maggiori, clinicamente rilevanti durante la terapia anticoagulante
- Mortalità durante il follow-up
- Derivare uno score sulla base dei fattori di rischio identificati e valutare l'**applicabilità dello score** in una coorte prospettica, ovvero
  - **prevedere le complicanze e l'aggravamento delle condizioni generali**
  - **identificare il grado di instabilità clinica del paziente**
  - determinare la gravità e la criticità della persona assistita
  - prevedere l'instabilità del paziente, cercando di prevenire un peggioramento, o una condizione irreversibile, segnalando al clinico la necessità di modificare le cure

CAT-Ther: Dati preliminari

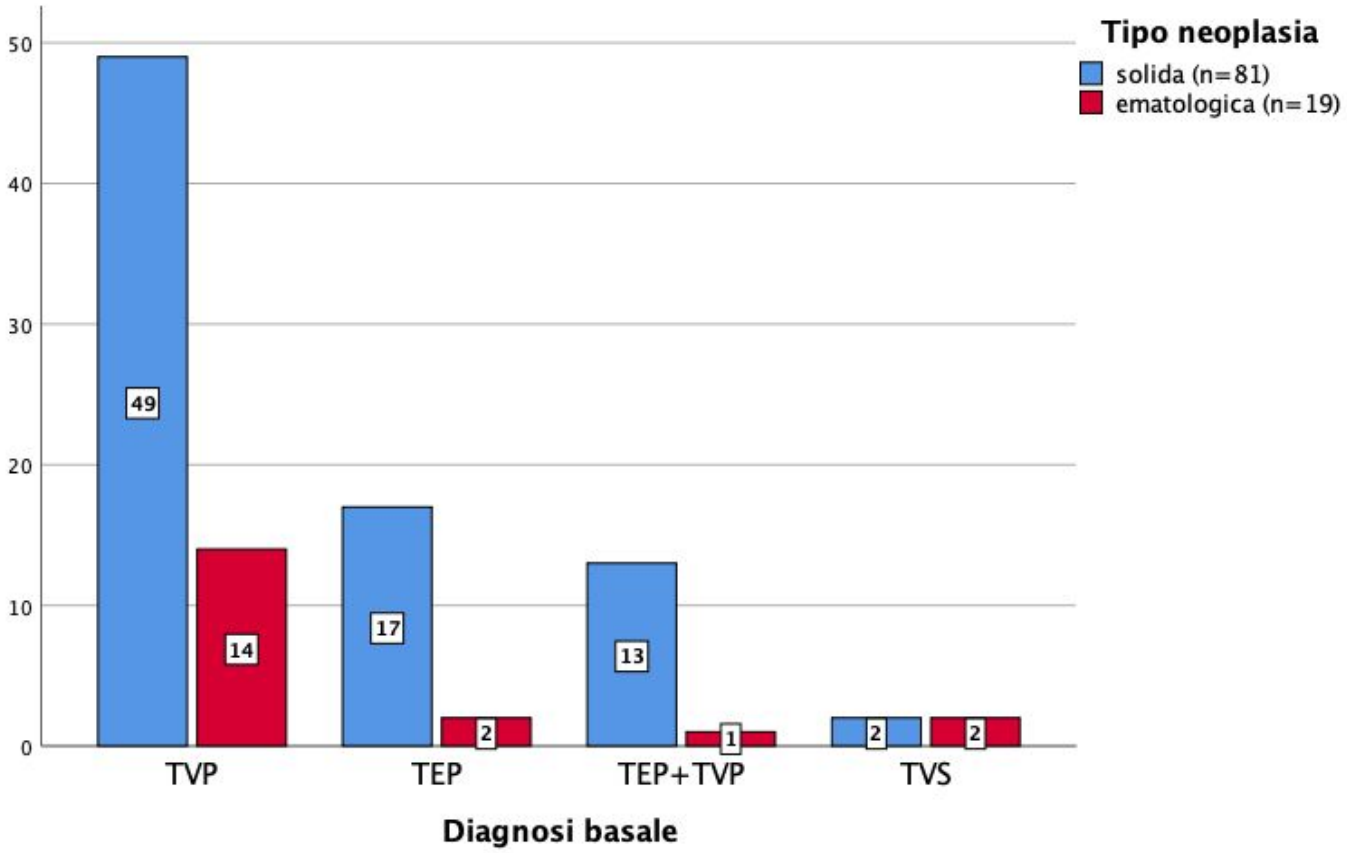
Sono stati esaminati 382 pazienti maggiorenni inviati per sospetto tromboembolismo venoso presso la *SSD Angiologia e Malattie della coagulazione* dell'IRCSS AOUBO dal 21/09/2018 al 19/12/2022.

In 100 pazienti è stata posta diagnosi di TEV in corso di neoplasia.

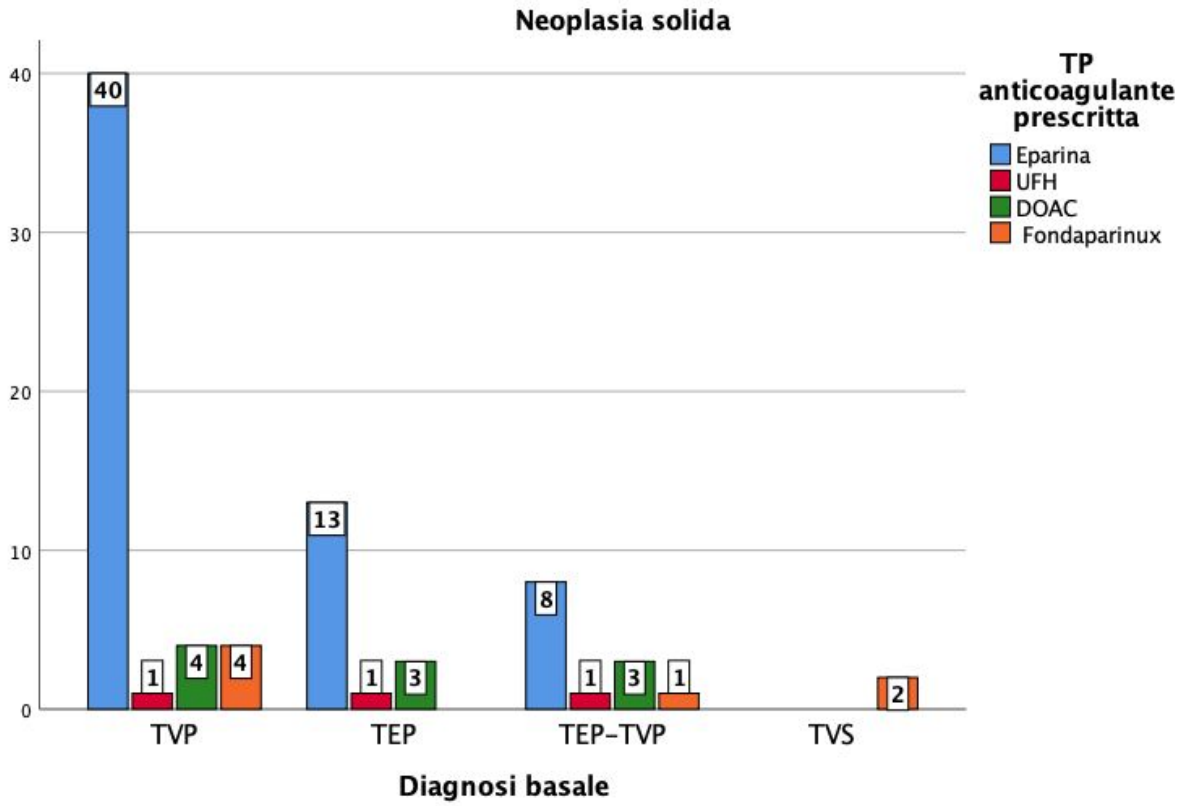
Dati al controllo basale	
Neoplasia *(n=100)*	81 solida ▪ 19,8% (n=16) tumore del polmone ▪ 17,3% (n=14) tumore della mammella 19 ematologica
Stadio della neoplasia *(n=100)*	50 stadio avanzato di malattia neoplastica
Sesso *(n=100)*	49 uomini 51 donne
Età: anni *(n=100)*	64,98 ± 13,55 / 68,27 / 18,03 - 89,47 *media/mediana/DS*
Punteggio medio WS	3
Terapia anticoagulante domiciliare *(n=19)*	68,4% EBPM 21,1% DOACs 10,5% TAO
Insorgenza dei sintomi *(giorni prima della visita di controllo)*	14 ± 9 / 20 / 0 - 21 *media/mediana/DS*

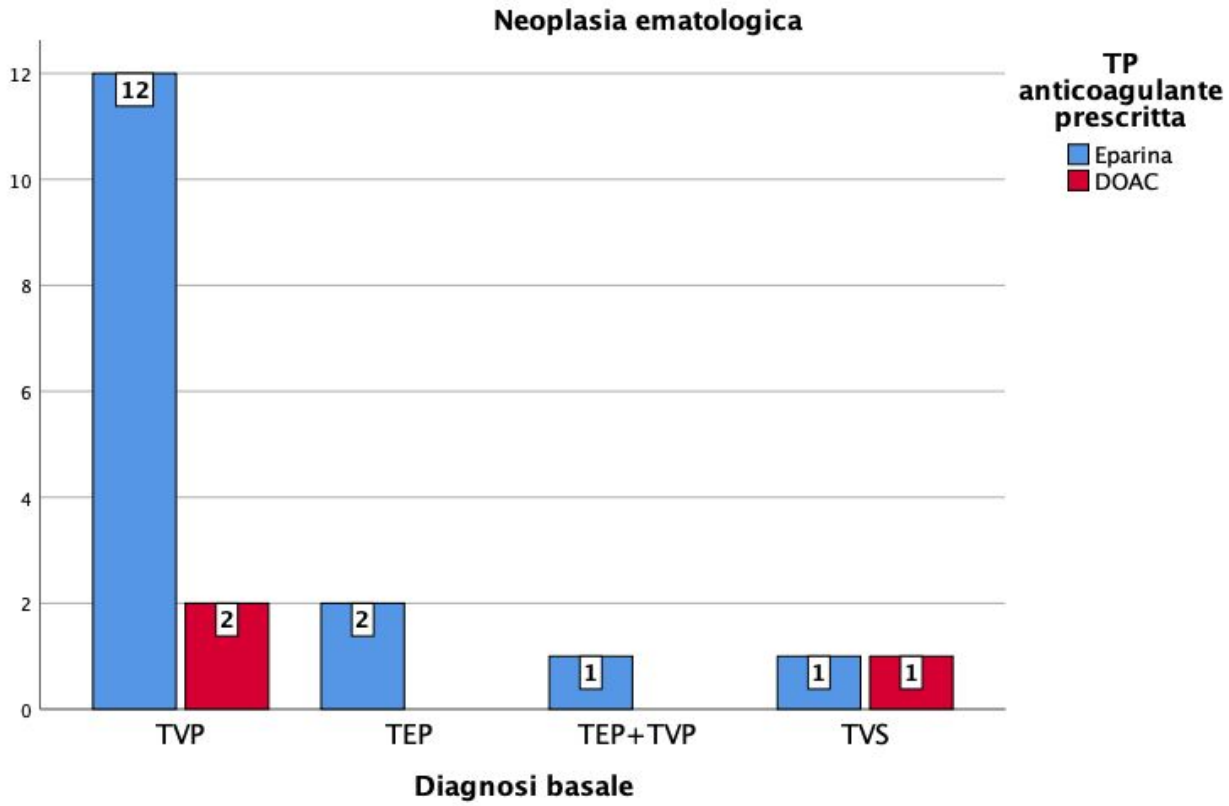
CAT-Ther: Risultati preliminari

ALLA DIAGNOSI		
Localizzazione	Pazienti con **neoplasia solida**	Pazienti con **neoplasia ematologica**
TVP	60,5%	77%
TEP isolata	21%	11,1%
TEP + TVP	16%	5,6%
TVS	2,5%	5,6%



CAT-Ther: Risultati preliminari





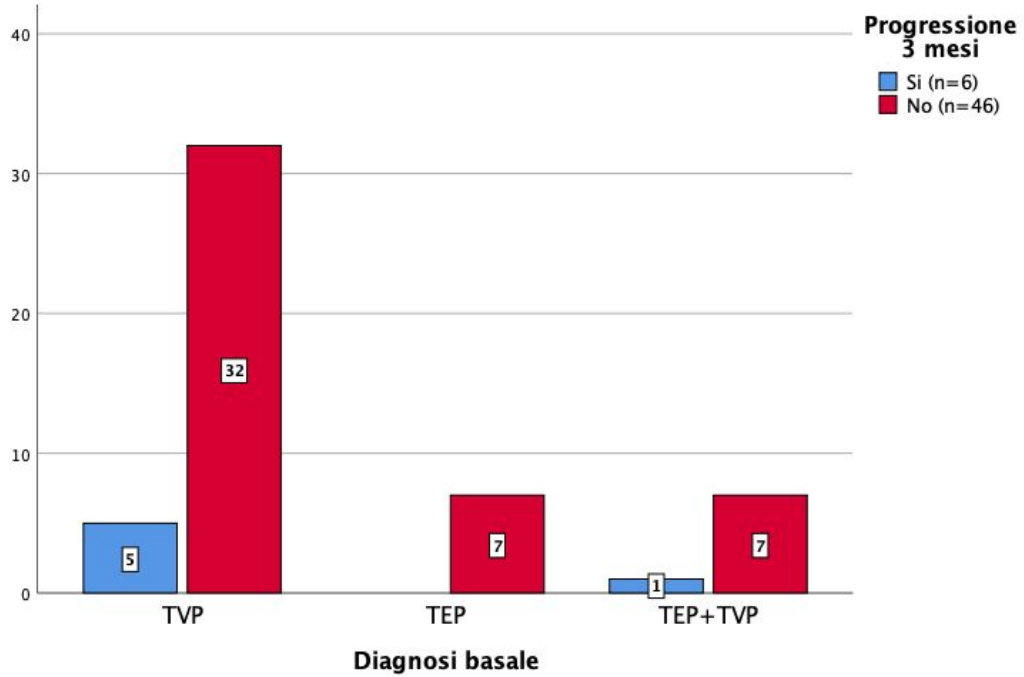
A 77 pazienti è stata prescritta come terapia eparina a basso peso molecolare, a 13 sono stati prescritti DOACs, a 7 un inibitore selettivo del fattore Xa (Fondaparinux) e solo a 3 pazienti è stata somministrata eparina non frazionata.

CAT-Ther: Risultati preliminari

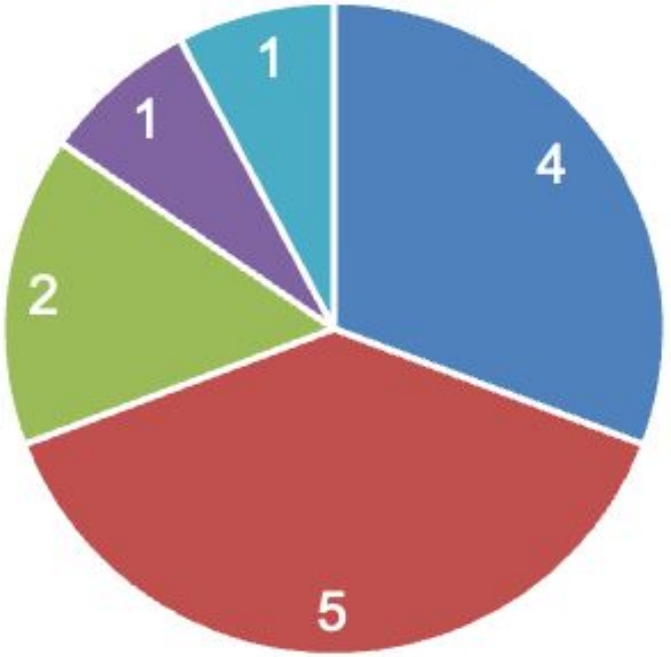
CONTROLLO A 3M

N=52

	TVP arti inferiori	TEP + TVP
RICANALIZZAZIONE COMPLETA *(o presenza di residuo minimo)*	86,5% *(N=32)* ▪ 24 solida ▪ 8 ematologica	87,5% *(N=7)* ▪ 6 solida ▪ 1 ematologica



Complicanze a 3M

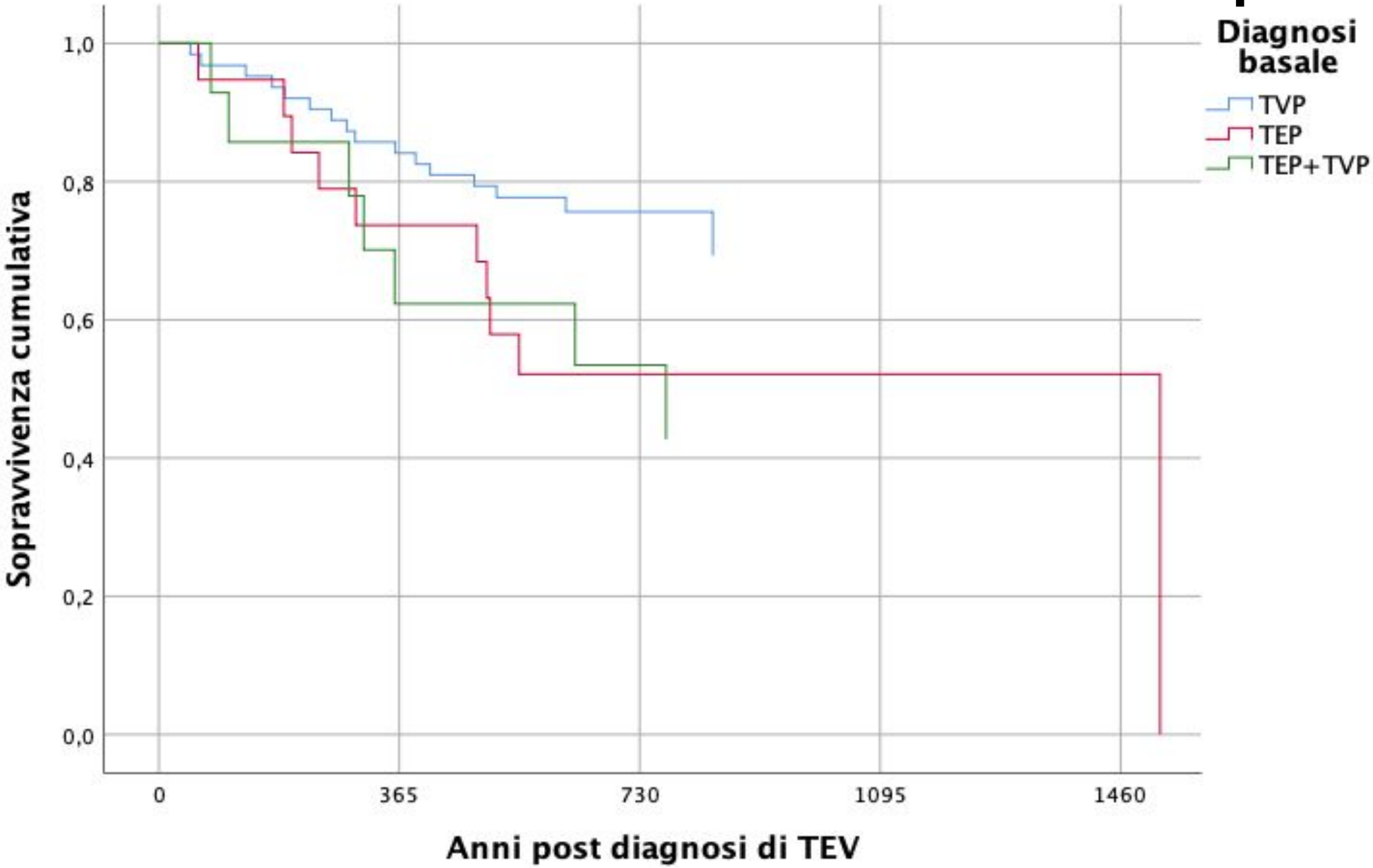


TVP stabile
Emorragia maggiore
Decesso
TVP stabile + Emorragia maggiore
TVP stabile + Emorragia maggiore + Decesso

Il sanguinamento maggiore è di solito definito come un **sanguinamento fatale** o la **riduzione dei valori di emoglobina di almeno 2 g/dl** o la **trasfusione di almeno due unità di sangue** o un **sanguinamento sintomatico** in aree e organi critici come il sistema nervoso centrale, il tratto gastrointestinale e lo spazio retroperitoneale

Complessivamente durante il periodo di osservazione il **trattamento con EBPM è stato prescritto all'83,8%** *(n=31/37)* dei pazienti con diagnosi di TVP, al 100% *(n=7)* dei pazienti affetti da TEP e al 62,5% *(n=5/8)* dei pazienti con contemporanea diagnosi di TEP e TVP.

CAT-Ther: Risultati preliminari



CAT-Ther: Conclusioni

Nonostante sia consolidato nella pratica clinica e in letteratura l'utilizzo degli anticoagulanti, quali EBPM o DOACs, in pazienti neoplastici con diagnosi confermata di tromboembolismo venoso si rende necessario identificare i pazienti a rischio di recidive tromboemboliche e di complicanze emorragiche per fornire un **approccio terapeutico più mirato**, **efficace** e **sicuro** per il trattamento delle *Cancer Associated Thrombosis.*

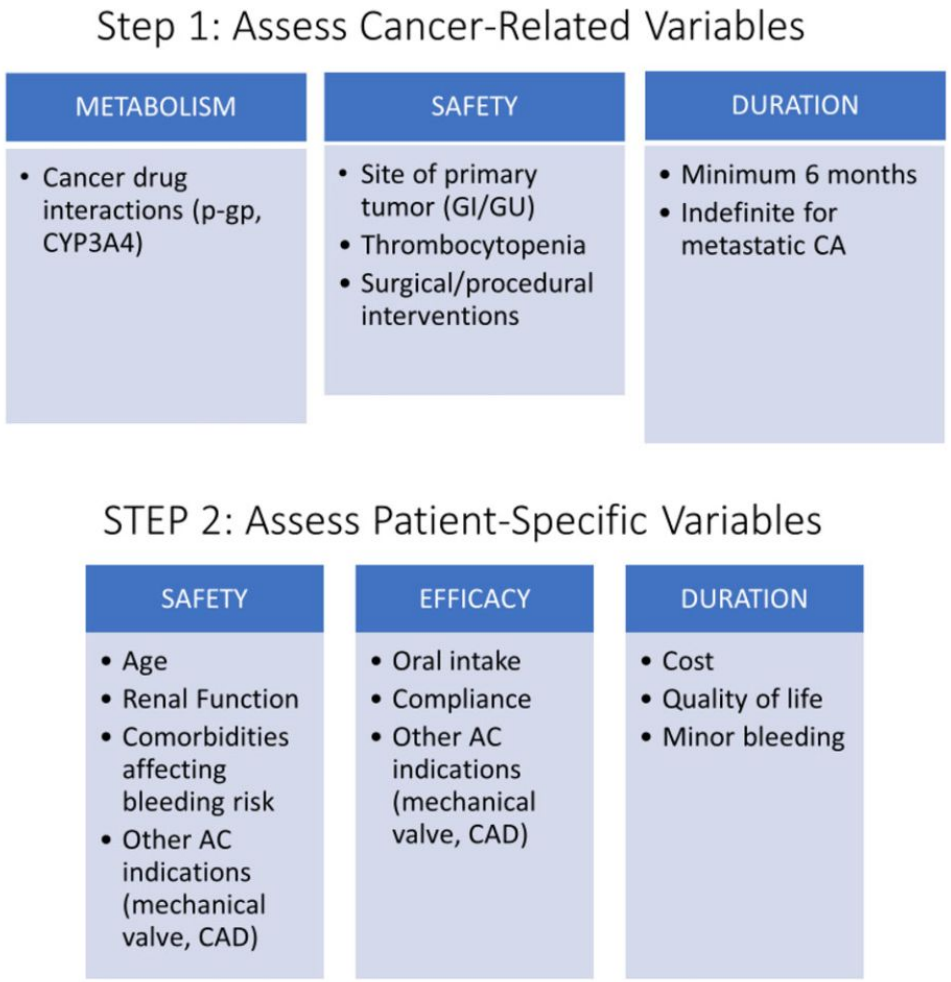


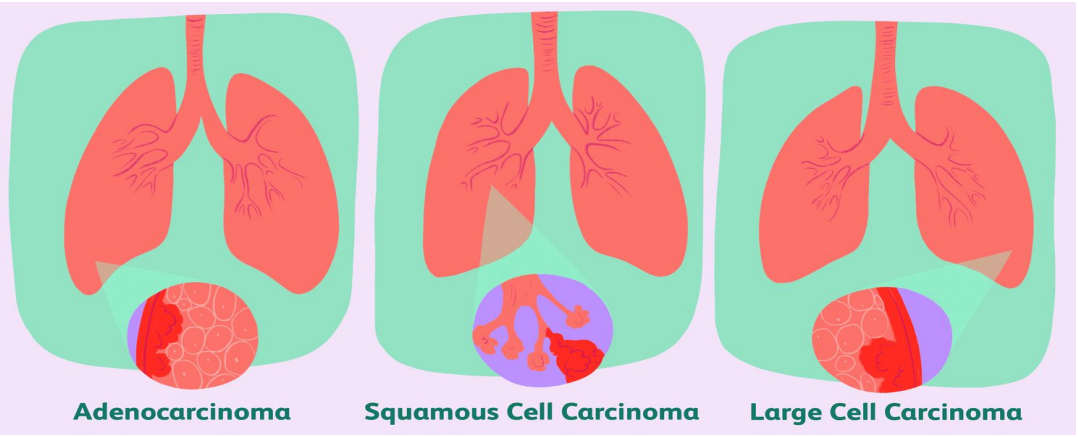
Figure 1. Two-step approach to choosing between three available classes of anticoagulants (direct oral anticoagulant, low-molecular-weight heparin, or oral vitamin K antagonist). Abbreviations: AC, anticoagulation; CA, cancer; CAD, coronary artery disease; GI, gastrointestinal; GU, genitourinary; p-gp, P-glycoprotein.

Treatment of Cancer-Associated Venous Thromboembolism with Low-Molecular-Weight Heparin or Direct Oral Anticoagulants: Patient Selection, Controversies, and Caveats. *Oncologist. O'Connell C et al.*

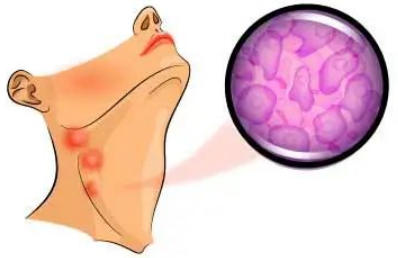
CAT-Ther: Limiti e Prospettive Future

- Pazienti affetti da **neoplasie estremamente eterogenee** tra loro per sede, istotipo, mutazioni genetiche, stadio e comorbidità
- Studio retrospettivo
- La valutazione della risposta al trattamento prende in considerazione il residuo trombotico alla CUS, **metodica operatore-dipendente**
- Pochi dati raccolti raccolti fin ora

- Completare la raccolta dei dati retrospettivi e implementare quella dei dati prospettici
- Stratificare meglio la popolazione
- Valutare un follow-up più lungo




Leukemia


Lymphoma


Myeloma

Grazie per l’attenzione